EXHIBIT C

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

In Re: Methyl Tertiary Butyl Ether ("MtBE")
Products Liability Litigation

MDL No. 1358
Master File C.A. No.
1:00-1898 (SAS)

This document relates to the following case:
City of New York v. Amerada Hess Corp., et al.,
04 Civ. 3417

EXPERT REPORT OF KATHLEEN M. BURNS, Ph.D.

Methyl Tertiary Butyl Ether in Drinking Water and Public Health Protection

168 Burlington St.
Lexington, Massachusetts 02420

Kathleen M. Burns Ph.D.

Signature

February 6, 2009

Date

TABLE OF CONTENTS

I. Qualifications

My name is Dr. Kathleen Burns. I have been retained by the New York City Law Department in collaboration with Sher Leff, LLP to evaluate the public health issues related to MTBE in wells owned by the New York City and located in Queens. I have been asked to consider potential public health issues if the wells are put into service for New York City residents, and past actions regarding public health issues by companies that have been involved in MTBE manufacture. This report and any testimony I provide in this case relies on scientific and other factual information, my previous work on MTBE, and my evaluation of new information obtained in order to prepare this report.

I have education, training and work experience in the areas of toxicology, epidemiology, public policy and public health. I received a Bachelors Degree in Biology (1977) and a Masters Degree in Social Sciences both from the University of Chicago (1981). I received a Ph.D. in Public Health from the Division of Environmental and Occupational Health Sciences at the School of Public Health, University of Illinois Medical Center in Chicago (1985).

I have published books on toxicology and risk assessment and have written books for government agencies on risk management and risk assessment. I have worked as a scientific and policy consultant since 1987, serving primarily federal and state agencies and non-profit organizations. My work has focused on toxicological, epidemiological and regulatory evaluations and the development of policy options to manage the public health issues arising from air, water, soil, product and food contaminants. I managed analyses and drafted technical support and guidance documents for USEPA water, air, product, and public disclosure regulations, and elicited information from companies regarding performance and stakeholder input on policy options.

In my work for USEPA I developed new methods to utilize pollution, demographic, and scientific databases in public health and environmental impact evaluations, and developed public information resources to inform local, state, and federal agencies, and communities about chemicals released into the environment. I served as an expert witness for the US Department of Justice on air pollution cases, a consulting expert on private litigation regarding prenatal exposures to chemicals in the workplace and from products, and potentially related birth defects. I recently served as an expert in water contamination litigation, including the MTBE Suffolk County Water case.

In 2005, I founded Sciencecorps, a small volunteer organization that provides technical assistance on scientific and medical issues to communities and organizations addressing environmental pollution and product and workplace chemical hazards. Our work ranges from hazard evaluation assistance to disabled World Trade Center responders to epidemiological studies of children's health in eastern Russia. I provide technical review of legislation and implementation plans, and have drafted bills and other policy tools in support of public health improvements. My CV is provided in Appendix B and contains a list of recent projects and publications.

In 1991 I became concerned about health hazards that might be posed by MTBE after reviewing study data that I received as the lead health consultant on a USEPA public-private sector pilot

project involving refinery emissions. In conjunction with that work, I requested and received toxicological studies from the MTBE Task Force. The few studies I received raised serious concerns regarding potential health risks posed that might result from MTBE exposures, including blood disorders and nervous system damage and disruption. Additional technical data that I located included evidence of difficulty cleaning up water contamination in New Jersey. I submitted a short memo to USEPA in 1991 and wrote portions of the pilot project multi-volume report on refinery emissions.

In 1995, I was asked by USEPA's Office of Water to review and upgrade a draft MTBE drinking water document. That review perpetuated my concerns regarding MTBE's potential to cause human health problems. The scientific literature I have reviewed in the intervening years has sustained those concerns.

In 2006, I was asked by a law firm representing the Suffolk County Water District to review all health-related studies, the availability of health-related evidence, and actions of the oil companies involved with MTBE in response to the evidence of potential health hazards. I submitted a report in January of 2007 and later that year a response to the Defendants' rebuttal.

From a public health and toxicological perspective, it is my opinion based upon the evidence I have reviewed over many years that MTBE poses a strong potential to harm the public and that this potential has been predictable from the scientific information available to industry for more than two decades. The expert testimony I provide in this report is based upon my knowledge of toxicology, public health, and environmental regulatory development, product safety, and a review of the data and facts related to MTBE. All of my opinions as set forth herein are based upon a reasonable degree of scientific certainty. A copy of my CV is provided in Appendix B.

Fee Disclosure: I am compensated at the rate of $150 per hour for expert report preparation and document review. I am compensated at the rate of $250 per hour for testimony, depositions, and related activities.

II. Opinions

I have been retained by counsel to review the available information on MTBE and to provide an opinion as to the potential health effects, if any, of MTBE. I have also been asked to provide an opinion on the nature, timing, and communication of health-related information by industry[1], industry and government's public actions regarding MTBE contamination of drinking water in the United States, and on the actions of water providers in response to MTBE contamination.

In formulating my opinions and preparing this report, I have relied upon the following:

- My experience and training in the fields of public health, public policy, toxicology, epidemiology,, biology, risk assessment and hazard evaluation, and product stewardship.
- The scientific studies, government reports, and other documents listed in the attached bibliography.

My opinions are as follows:

Based on substantial scientific evidence, MTBE in drinking water is likely to pose health hazards[2] to some members of the public. MTBE caused cancer in animal models that are relied upon by the US government to predict cancer in humans. MTBE damages genetic material and caused other serious health problems in multiple species that the US government relies upon to evaluate the potential for birth defects and other types of damage. There is no credible or proven "safe" level of MTBE exposure and there is substantial and evidence that no safe level exists.

Before MTBE was introduced as a gasoline additive in 1979, industry was aware of MTBE's potential for causing serious health effects by virtue of the large body of medical knowledge available on ethers and from their own early studies. Industry knew by 1980 that MTBE posed health hazards and could contaminate water, based on the scientific information they had and their own experience in the field. Additional evidence regarding MTBE's potential for serious health damage and widespread contamination was available prior to industry's selection of MTBE as a fuel oxygenate to meet RFG requirements in the early 1990s.

Industry failed to act as good product stewards by (1) delaying or failing to perform additional experimental studies when the evidence indicated that MTBE demonstrated the potential to

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1. For purposes of this report, in order to simplify statements, "industry" is used herein to specify members of the petroleum industry who manufactured and blended MTBE named as defendants in this case.

2. The term "hazard" is used broadly in this report to refer to all types of physical harm, including birth defects, developmental abnormalities, cancer, and damage to organ systems and basic physiological functions in the body. I have chosen to use the concept of hazard because it is a well founded idea that has been used in public health evaluations and protective public health policies for many years across many parts of the globe.

cause health hazards; (2) failing to communicate this potential for harm to regulators or the public in a timely manner; and (3) skewing and/or misrepresenting the evidence of the potential for health damage in order to perpetuate the use of MTBE.

Industry was not a good product steward because they elected to continue and increase the use of MTBE in gasoline in the 1990s in spite of growing evidence of health hazards and foreseeable extensive contamination of water.

Drinking water standards for MTBE are developed through deliberations where public health is traded against other considerations. The standards vary considerably, affording varying levels of protection and it is my opinion that they do not comprehensively protect the public from harm.

The seriousness of the health hazards posed by MTBE requires the maximum protection from exposure that is possible. It is my opinion that water providers are acting in a responsible and reasonable manner in seeking to minimize public exposure to MTBE.

reproductive function.

Billitti also found that two metabolites of MTBE, TBA and TBF (tributyl formate) increased testis weight. As with the results above, this study provides evidence that MTBE can cause abnormal changes in the male reproductive system. The findings above are consistent with the results of studies from the early 1980s that showed MTBE had a potential to harm reproductive function. If the earlier studies had been taken seriously and the problems had been investigated fully, it is highly likely that widespread MTBE use and contamination would not have occurred.

Quality Control

Dr. Kirwin, was an industry toxicologist in charge of health and safety review of MTBE and participated in API and other industry meetings on MTBE's health effects. He made observations about many of the problems regarding the reproductive and developmental toxicity studies that were sponsored by the Defendants. He noted an inconsistency when the quality control auditor reported that the study laboratory erred in reporting no adverse effects, when there were in fact effects from MTBE (page 237 May 31, 2007 Kirwin Deposition). Dr. Kirwin identified the loss of animals as "a significant error" because it could result in a miscalculation of how many animals died (age 238, ibid). He also noted that not being able to determine which litters had missing pups or the number that were missing, or whether they were missing because they had abnormalities were "important quality control assurance concerns" (page 241 ibid).

Dr. Kirwin stated that that some of the problems identified in the internal quality control reviews would not have been sent to the reviewers within the government (page 243 ibid). In discussing peer review, he stated, "they (the reviewers) get the paper that is intended to be published." (page 303 ibid, reiterated page 25, June 2, 2007). In other words, the reviewers of a prospective journal article do not get information such as quality control reports on study problems, lost animals, misidentified animals or other reports that can call into question the accuracy of a study, unless the study authors chose to report those problems within a paper.

In fact, most of the numerous problems in the reproductive and developmental toxicity studies that were identified by quality control reviews and reported internally to the Defendants were not discussed in the papers that were published by the Defendants' scientists (e.g., Biles, Conway). Clearly, publication does not guarantee adequacy of the studies or accuracy in results. The scientists submitting the papers are relied upon to be accurately reporting their observations, and any problems that occurred during the studies.

The very serious nature of the problems that were observable in the Defendant's studies in spite of the limitations in the study is a very important issue when considering the developmental hazards of MTBE. Yet these studies were repeatedly referred to by the Defendants as showing that MTBE did not cause any particular hazards to pregnant women or children. In the absence of full information on the studies, having only the very limited information in the journal articles, this erroneous information was perpetuated and has misled the public regarding the true nature of the studies.

The reality of the situation did not suit the needs of the Defendants and so was not disclosed in

the journal articles that were published. The very serious results obtained in the developmental and reproductive toxicity studies, ranging from bone formation defects up to death, were not addressed adequately. Dr. Kirwin sums up his groups' efforts regarding MTBE in response to a question about whether he was asked to reevaluate MTBE:

> "I don't know that I was asked to reevaluate it. We just continuously, through the early '80s were working with trade associations to develop toxicology testing programs so we could confirm the health safety of the chemical."
>
> (Kirwin, page 71 May 31, 2007 deposition)

In fact, they did not take seriously the information coming out in the developmental, reproductive, or other studies when electing to commercialize MTBE. What they did do was confirm their earlier assertions of safety. This did not serve the public well.

Dr. Kirwin was involved in the design of the studies, including a determination of how many animals would be used (page 156, May 31, 2007 Kirwin Deposition). However, when the issue of USEPA animal testing guidelines was brought up in his deposition (e.g., how many study subjects should be used to insure that a study can achieve statistically significant results), Dr. Kirwin was not aware that there were specific protocols. The fact that many of the study outcomes appear serious but do not achieve statistical significance is not surprising in light of Dr. Kirwin's statement.

As noted above, there are many federal policies designed to protect children, who are considered more vulnerable to chemical exposures in general. The position of industry with respect to children and MTBE may be better understood in the words of one of their own scientists who directed health-focused research in the 1980s. Speaking to the issue of protecting the public, taking into consideration effects on the general public versus workers, Dr. Kirwin stated: "There's no difference. No difference at all." (Kirwin, page 129, May 31, 2007 deposition). Obviously, the majority of those who work in the field of children's health, and many who work in the field of adult health would not agree that a fully-grown, healthy adult worker is identical to the varied members of the general public.

Neurotoxicity and Development.

A significant gap in the developmental toxicity data that has never been addressed is the area of nervous system damage during development. Based on the considerable information available in pediatric neurotoxicology (harm to the nervous systems of children), Dietrich et al (2005) stated that:

> "The developing human central nervous system is the target organ most vulnerable to environmental chemicals."

The desire to protect children from neurotoxic chemicals is both well-founded and reasonable. The lack of research into neurological damage by MTBE, given its well-established neurotoxic capabilities, is reason for considerable concern, especially in light of widespread population exposures. Concerns regarding increased rates of neurological diseases in children have raised

awareness of the problems associated with exposure to neurotoxins in early life.

Given the considerable evidence available early on regarding the neurotoxic properties of MTBE and the likelihood that public exposures would occur, industry should have carried out careful studies of neurotoxic impacts prior to adding MTBE to gasoline. Certainly, after receiving the results of the developmental studies described above and before widespread contamination had occurred, it would have been the responsible thing to do.

Recent Evidence Regarding Damage to the Male Reproductive System
In 2008 a study was published that provided additional evidence that males exposed to MTBE were at risk for damage to their reproductive system. Experimental evidence from short term (2 to 4 week) exposure studies found physical damage to the reproductive organs (Li et al, 2008). The tissues in the tubules used to carry sperm were damaged. The sperm themselves were also abnormal. Additional information was obtained on disruptions in numerous male hormones, as described below in the section on hormone disruption. Thus, the problems initially indicated in industry studies in the early 1980s have been confirmed. It is inexcusable from a scientific vantage point that the accurate information was not provided at that time, and that follow up did not occur quickly. MTBE's potential to disrupt and damage the reproductive system of males and the lack of any known safe level at which this will not occur, is a compelling reason to prevent public exposure to MTBE.

Summary Regarding Developmental and Reproductive Damage
The key conclusions that I draw from the information above are as follows:

- Studies of MTBE's developmental and reproductive toxicity during the 1980s provided evidence of many types of harm to the developing individual. The results in industry reports were misleading in stating that MTBE was not a developmental or reproductive toxin. This seriously undermined the ability of the public to be warned of the hazards of MTBE.

- The industry-sponsored studies were weak and in some cases had serious quality control problems. If these studies were done properly, they would clearly show a broad array of developmental damage based on the evidence that was available to industry in the 1980s.

Given the spectrum of developmental and reproductive hazards outlined in this section, it was not responsible to allow public exposures to MTBE to occur through introduction of MTBE to gasoline. Regarding the potential harm to children, it is both reasonable and prudent for water purveyors to seek to protect the public by minimizing exposure to MTBE to the best of their ability.

E. Cancer

The potential for MTBE to cause cancer has been evaluated in three long term exposure studies and in many follow up evaluations of specific issues related to carcinogenic potential. This highly

contentious area continues to be the subject of study, evaluation and scientific articles regarding the interpretation of data.

Basic Evidence that MTBE Causes Cancer.

The ability of MTBE to cause cancer has been researched in three basic studies of long term exposure and cancer outcomes. The basic cancer studies were carried out using both oral exposure (ingestion of MTBE) and inhalation of MTBE. This is important because some chemicals cause cancer when exposure occurs via one route, but not another. MTBE caused cancer in both exposure routes that were studied. The studies were performed at different laboratories by different researchers and studies were carried out on male and female subjects in two species. Table 4 lists the authors, study subjects, and types of cancer observed in the three basic cancer studies that were carried out. These formed the basis for discussions of MTBE's cancer-causing ability and for government actions.

Table 4. Studies of the Carcinogenicity of MTBE

RESEARCH AUTHORS	STUDY SUBJECTS	ORGAN SYSTEMS AFFECTED	STUDY SPONSOR	RESULTS DATES* (PUBLICATION)
Burleigh-Flayer, Chun, Kintigh	mouse	liver	industry	1991 (1997)
Burleigh-Flayer, Chun, Kintigh	rat	kidney, reproductive (testicular)	industry	1991 (1997)
Belpoggi, Soffriti, Maltoni	rat	reproductive (testicular), hematopoietic (lymphoma and leukemia)	Ramazzini Foundation	1995

* Dates results were given to study sponsors followed in parenthesis by date of publication in peer-reviewed journal, if those differ substantially. Burleigh-Flayer, Dodd, Bird, and Ridlon initially reported results of the mouse and rat studies 6/18/91, and they were released by Burleigh-Flayer, Chun and Kintigh as separate unpublished studies in 1992. They were published in 1997 in the peer-reviewed literature.

Study results showing statistically significant increases in cancer in two or more species meet important criteria established by USEPA for determining that a chemical is likely to pose carcinogenic risks to humans (USEPA, 2005). The observation of multiple types of cancers in multiple species that were exposed through different pathways provides additional information in support of a determination that a chemical is a carcinogen. The three studies listed in Table 4 formed the foundation for USEPA's past deliberations regarding MTBE's cancer causing abilities and some regulatory decisions. They are also fundamental to the decisions of many states, including New York, regarding MTBE in drinking water. The USEPA and state evaluation of MTBE regarding its cancer potential and their policy decisions are discussed in more detail below.[17]

17. The determination of MTBE's status as a carcinogen was and is very important in the context of policy and regulations, and this is discussed in Section V.

The cancer studies yielded differing results, but that is not surprising, given the different conditions of exposure and durations of the studies. The Belpoggi, et al study observed the animals until they died (a lifetime study), unlike the industry-sponsored studies. The lifetime observation provides an opportunity to observe tumors that occur later in life and that only occur at statistically significant levels when older animals are observed. This facilitates the identification of more tumors and different types of tumors than might otherwise be observed and may lead to higher estimated cancer potency for some chemicals (resulting in stricter controls). This information is undesirable if the goal is to keep a chemical on the market. However, it is optimal to fully evaluate potential public health impacts because we do care about health problems that may occur later in life.

It is well established in the cancer epidemiology literature that most types of cancer occur more frequently as people age. With rare exception, cancers are far more common among people in their 60s and 70s, than in young or middle-aged people (National Cancer Institute, SEER Database, available online at www.nci.gov). This fact was emphasized by Dr. Carroll Kirwin, Director of Health and Safety for many years at Phillips and the toxicologist who oversaw their evaluation of MTBE's health hazards. He recently stated with respect to doing chronic (long-term) studies that:

> Cancer requires lifetime exposures in these animals to reveal it. Cancer, as everybody knows, in general cancer is a disease of the aged, more old people get cancer than young people."
>
> (page 36, June 1, 2007 Kirwin)

Thus, the value of a full lifetime animal study is that it can identify the rate of occurrence of cancer, and the types of cancer more completely than studies that are terminated earlier in life. The Belpoggi et al (1995) study provides better insight into likely effects of MTBE, and their subsequent evaluations and publications regarding specific aspects of their study provide additional insights. In combination with the industry-sponsored studies that found cancer in two species, we have a group of studies that implicate MTBE as a carcinogen, and require that public exposures be minimized.

The last column in the table shows the dates that the study results were released to the study sponsors, followed by the dates that results were published in peer-reviewed journals that provide public access to the information. It is notable that there was a substantial delay between the first reporting of results of the industry-sponsored cancer studies in 1991, and the publication of the results in a manner that was accessible for review and use by the scientific community (1997). During that time period, MTBE moved from relatively limited use as an octane enhancer to very widespread use as the industry's oxygenate of choice to comply with RFG requirements. Industry elected to go forward with a substantial expansion in the production and distribution of MTBE in spite of the results of their own cancer studies.

Additional information that supports the positive cancer findings is discussed below under the heading "Mutagenicity and Genotoxicity". This information provides scientific insights into how

MTBE causes cancer. The supporting evidence makes it clear that MTBE causes damage at the cellular level, where cancer begins, and it does so through damage that we know can cause cancer. Overall, the objective evidence that MTBE can cause cancer is substantial and persuasive.

Additional Studies, Evaluations, and Debates Regarding the Basic Cancer Studies

The publication of the basic long term exposure studies that found MTBE caused cancer were followed by many papers discussing the results and reporting on new results that considered specific aspects of the types of cancer that were observed. Studies to evaluate mechanisms of carcinogenic action, provide more detailed pathological characterization of the tumors observed, and more fully evaluate the nature of the carcinogenic response. Many of these were funded by industry. Numerous studies in 1996 alone evaluated aspects of liver cancer (Moser et al, 1996), kidney cancer (Prescott-Mathews et al, 1997) and kidney cell proliferation, a precursor to cancer (Poe and Borghoff, 1996).

Industry has consistently maintained that MTBE was not carcinogenic to humans on the basis of a range of arguments addressing each of the types of cancer identified in the basic studies. In the discussions of these cancer studies, communications with the USEPA, and in scientific journals, industry has argued that MTBE does not pose a cancer risk to humans, in spite of strong evidence to the contrary. The basis for most of the arguments hinge on detailed and specific scientific characteristics of the tumors, mechanisms of tumor formation, characteristics of specific species, and statistical and quantitative issues. I have carefully reviewed these arguments and find them to be of questionable scientific validity and as such, that they do not undermine the need for protection from MTBE as a carcinogen. Of the dozens of articles on this issue, I have described a few below that are indicative of the general approach taken by industry to discount their own two studies and the additional study that found cancer was caused by MTBE.

A paper published by industry scientists in 1997 (McKee et al) argued that instead of using the rates of cancer that were found in control subjects in the industry study carried out in rats, they should rely on older studies that found different rates. This would allow them to dismiss the testicular tumors that occurred at statistically significant levels in their study among animals exposed to MTBE. It is both inappropriate and misleading to dismiss the results of a study by simply referring to what has happened in the past. In their study, where the exposed and unexposed animals were all treated in the same way and were from the same strain (being genetically nearly identical), a comparison of cancer occurrence among the animals was the most relevant. That comparison found significant results.

Dismissing the results based on historical data is not justified. In their "Guidelines for Carcinogen Risk Assessment", USEPA states the following:

> Generally speaking, statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average. Random assignment of animals to groups and proper statistical procedures provide assurance that statistically significant results are unlikely to be due to chance alone.

(USEPA, 2005).

USEPA's statement echoes long-held scientific practices and indicates that the observation in 1991 of testicular cancer should have been taken far more seriously by industry if they were concerned about protecting the public. It is important to also note that testicular tumors were reported in the cancer study by Belpoggi et al (1995). This added corroborating evidence from industry's own study regarding testicular cancer, through similar findings in another study at a different laboratory carried out by a different set of researchers.

Another issue that has been raised involves alpha-2-microglobulin and kidney cancer. Industry argues that the kidney cancers should not be considered relevant because of this issue as it relates to male rats. In response to this, the National Science and Technology Council's team of government scientists studying the MTBE scientific evidence asserted that the industry arguments were only relevant to male rats. They noted that alpha-2-microglobulin was not involved in some important aspects of kidney damage in the study subjects (National Science and Technology Council, 1997).

More recently arguments have been made that because animals were followed for their entire lifespan in the Belpoggi et al study (1995), a calculation was required to adjust for survival times and subsequently modify the study's results. Industry scientists used a lifespan of 174 weeks in their calculations, which is much longer than the animals typically live. Two years, or 102 weeks, is the standard laboratory observation period in a life time study. By choosing a nonsensical number, they were able to manipulate the calculations to show results were not significant (Goodman et al, 2008).[18]

In practice, the industry scientists' calculations made no sense. The inappropriate assumptions they used were identified and described by cancer scientists working for the US National Institutes of Health, including the Director of the Office of Risk Assessment Research and the Associate Director for Chemical Carcinogenesis at the National Institutes of Environmental Health Sciences (Kissling et al, 2008). The government's top cancer scientists point out that the actual times of death that could have been used by the industry scientists to correctly use incorporate survival information have been available to the public for some years and are posted on a public website with the results of the study.

The government cancer experts carried out an analysis using a survival adjustment, but also employing a more standard length of life (the standard two years considered in most cancer

18 The paper asserting changes were needed in calculations can be justifiably attributed to industry, though the affiliations of the authors were not oil companies, they were consulting firms. The acknowledgements section of the paper contains a disclosure that has increasingly been required by journals in the last few years - a statement of where the funding for the work and development of the paper comes from. The acknowledgement states:

> "Financial support for the research and preparation of this paper was provided by a fund created by various members of the oil industry engaged in litigation regarding the use of MTBE in gasoline." (Goodman et al, 2008)

toxicology studies). They found that the reporting of an increase in cancer was correct. That the increases in tumors were statistically significant, and that the trend of increases in tumors with increases in MTBE doses, was also statistically significant. In other words, they found the study to be valid in providing evidence of cancer (Kissing et al, 2008).

The arguments industry has made with regard to testicular cancer, kidney cancer, and other evidence regarding cancer is typical of their actions to dismiss evidence of the harmful MTBE effects that were observed in their own studies and other studies. The common practice across many industries of creating scientific uncertainty to avoid regulation or responsibility, when in fact there is little uncertainty, has been well documented (Michaels, 2006) and is discussed below.

Early Studies Indicating Toxicity in Organs where Cancer was Found.
Supporting evidence clarifies how strong the overall body of evidence is with respect to MTBE's carcinogenicity. Supporting evidence from genotoxicity and mutagenicity studies are discussed in a later section. This section addresses early evidence of toxicity in those organs where cancer was later observed to occur.

An early industry-sponsored study of animals exposed for 90 days to MTBE found evidence of blood abnormalities, including decreases in red blood cells at all exposure levels after only 5 weeks of exposure. Other types of cells were also present at abnormal levels. Within the text of the study, the problems are discussed in detail. The study also found increased liver, kidney and adrenal gland weights. The study summary stated, "clinical pathological changes seen in the rats following MTBE exposure were related to stress." (Bushy Run Center, 1989; Neptun et al, 1989). However, increased weight is often related to pathology in an organ system, and so that type of finding is important to evaluate carefully and comprehensively.

In fact, the studies completed just two years after this study found liver and kidney cancer (as reported above, see Table 4).[19] The blood abnormalities that were observed involved the same system, the hematopoietic system, which is involved when leukemia and lymphomas occur. Clearly if the full potential for damage to these organs was evaluated early on, in a long term study for example, and that information was accurately communicated, it would have been possible to avoid contamination of drinking water with MTBE.

When I reviewed the results of the Bushy Run study in 1991 as a part of my work for USEPA on emissions from an oil refinery in 1991, I was concerned about the possible implications regarding aplastic anemia (a frequent precursor to hematological cancers) and about the potential for MTBE to cause such cancers. These study results should have created concern among industry's toxicologists, but they were neither acknowledged in a responsible manner, nor did industry take action to prevent public exposures by withholding commercialization until the potentially serious health issues could be fully explored.

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19 The study also found abnormal levels of adrenal and pituitary hormone levels, but the small number of animals in each group (10) made interpretation of this difficult. As with the other effects, the summary stated that these "appeared to be related to biological effects of stress."

F. Mutagenicity and Genotoxicity.

It is important to determine if MTBE can cause mutations, damage DNA, or damage the accurate reproduction of cells. While these changes occur at the microscopic level, they can be important to the health of a person because they can tell us whether birth defect that pass from generation to generation may occur, and if damage is likely to occur during development due to changes in the fundamental ways in which cells develop and reproduce themselves.

The genotoxicity of MTBE is relevant to evaluation of its carcinogenic potential because damage to genetic material is a well-established mechanism of cancer induction (Ward et al, 1994, USEPA, 2005).

Cancer is often described as a disease where cells replicate in an uncontrolled abnormal way. The ways that cell reproduction is damaged vary and many are described in detail in USEPA's cancer guidance document (USEPA, 2005). They can be distilled down to the basic idea that alterations in the timing and ways that cells replicate can lead to very serious changes at a microscopic level in cell tissues. These changes can result in the uncontrolled growth that we call cancer. There are many different types of tests that assess whether a chemical can damage cell's ability to reproduce accurately, and there are many ways that chemicals can do this. MTBE has been tested in many different types of studies, and the results are a mixture of positive and negative outcomes. That is not surprising, and does not undermine the value of the results that showed MTBE can cause damage to cell replication. It only requires one avenue to cause this damage in order to initiate cancer growth.

Early Evidence

Very early in the history of MTBE use an increase in mutations was observed in lymphoma cells (ARCO, 1980). The cells are part of the blood forming system and so this finding was very relevant to concerns about hematopoietic system cancers - lymphoma and leukemia. Industry dismissed the results based on the fact that the mutations occurred in a study where MTBE was metabolized. This means that the study created conditions similar to those in the human body to see what would happen if MTBE were metabolized. Often the metabolites of a chemical are more harmful than the original chemical before it is digested. In this study, the fact that mutations occurred under conditions designed to be similar to what happens when humans are exposed is very important and makes these results highly relevant.

A number of studies were carried out using the same method repeated many times in a mutagenicity test referred to as the Ames assay. This test did no yield results showing mutagenic potential, as the many entries in CDC's summary show (CDC, 1996). The results of the reproductive and developmental toxicity studies discussed above, where the number of pups who survived were reduced, and birth defects of various kinds were found would add weight to concerns regarding the results found in the ARCO, 1980 study. But the negative Ames studies were used to argue that MTBE did not have mutagenic or genotoxic effects.

Evidence in the early 1990s

In a study of genetic damage reported by Galvin et al, in 1994, animals were exposed to MTBE for five days. Their bone marrow was then evaluated for to see if chromosome damage had occurred. The results of the study are shown in Table 5. There was an increase in the number of abnormal cells as the doses of MTBE increased. The bone marrow is involved in the production of blood cells, and when leukemia or lymphoma occurs, these cells often show damage to the chromosomes.[20]

Table 5. Results of a Study of Chromosomal Aberrations in Bone Marrow Cells in Male Rats Exposed to MTBE for Five Days*

MTBE CONCENTRATION**	NUMBER OF ABNORMAL CELLS	MEAN PERCENTAGE OF ABNORMAL CELLS
0	13	5.2
800	14	5.6
4000	17	6.8
8000	18	7.2

* Based on Galvin et al, 1994. Five animals per study group were evaluated with 250 cells per animal reviewed.

** Concentrations are listed in parts per million

The results shown in Table 5 were not statistically significant, meaning that they did not pass a specific statistical test. It would have required many more study subjects to obtain results that passed the statistical test, if the trend seen in this study held. Even with an increase of 38% in the high exposure group, the statistical test was not passed. When this level of increase is not considered statistically significant, it suggests that the study design is not capable of capturing genuine effects in a scientifically meaningful way - i.e., by designating them as being significant. However, the increases in both the number of abnormal cells and the mean percentage of abnormal cells are clear and the results were important.

In this case, due to the importance of the observation of chromosomal damage, especially with such a short exposure period, industry should have carried out a study with an adequate study design - one with sufficient power to detect a statistically significant effect, or to prove that there was no effect, if that was the case. However, the study was not repeated with a stronger study design. Instead the study's authors, who were affiliated with Phillips, ARCO, and the Bushy Run Research Center, concluded that:

> MTBE did not produce statistically significant or exposure related increases in the incidence of chromosomal aberrations in the bone marrow cells of either male or female F-344 rats. Therefore, MTBE was not considered to be clastogenic in this in vivo test system.
>
> (Galvin et al, 1994).

20 The study only lasted for five days and that is too short a period of time for cancer to be induced. Cancer usually takes many years to develop to a clinically-detectable level following exposure to a carcinogen. So cancer was not evaluated in this study and could not have been.

The authors did not point out the increase they found in their results, nor did they state any concerns about repeating the study in their report. And follow-up communications in the scientific literature by authors from industry[21] restate the information in the quote above (McKee et al, 1997). They express no concern.

Ward and other scientists were asked to evaluate the existing studies on this topic (Ward et al, 1994). Their recommendations included the use of more study subjects. They also pointed to a specific toxicological feature that they felt was important - that care must be taken regarding the doses used in studies. They pointed out that formaldehyde, a chemical produced in the body when MTBE is metabolized, appears mutagenic "over a narrow dose range in some studies, and can only be observed under specific conditions," (Ma and Harris (1988); O'Donovan and Mee, 1993). The strong implication of this is that study design could undermine the ability to accurately evaluate MTBE.

Table 5 results are relevant to the observation of lymphoma and leukemia (blood-related cancers) in the Belpoggi study, because bone marrow is a key part of the blood forming system.

Recent Studies

In recent years, numerous researchers have published the results of many studies of MTBE's effects on DNA that show multiple types of damage. These are all relevant to cancer and to the potential for exposed populations to have heritable changes in their DNA that could cause birth defects.

Zhou et al (2000) reported in their study that MTBE caused "unscheduled DNA synthesis," meaning that it has the potential to cause DNA to act when it should not - leading to abnormal cell replication. They studied this in rat liver tissue because this was a tissue where cancer was caused by MTBE in the 1991 Burleigh-Flayer et al study. Cancer is often characterized as a disease where cells replicate in an uncontrolled way.

Zhou et al (2000) also reported an additional problem that is related to cancer. They found that MTBE both induced abnormal cell growth and inhibited the natural processes of cell death (apoptosis) used to remove abnormal cells. The lack of the body's ability to identify and remove cancerous cells is one key feature in establishing cancer. Consequently, apoptosis is very important and impairing it makes it easier for cancer to develop.

A study of MTBE by Yang et al (2005) found DNA damage in kidney and liver cells. These were consistent with the organs where cancer was observed.

Du et al (2005) likewise found that MTBE caused DNA adducts in the lung, liver, and kidney cells. DNA adducts are a type of DNA interaction that indicates the potential to cause cancer (USEPA, 2005). The results were found in the same organs that were found to have cancer in the two industry studies reported above (See Table 3 above).

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21 (Exxon Biomedical Sciences, Bushy Run Research Center, Phillips Petroleum, Oxygenated Fuels Association, and ARCO Chemical Company)

In 2007, Yuan et al, carried out additional work to find out how MTBE binds to DNA to form adducts at low doses. They found that a particular part of the MTBE molecule, the methyl group, forms the adducts with DNA. This type of improvements in the level of detail within the scientific evidence is an important part of the progression of medical science regarding MTBE and its carcinogenic characteristics.

In 2008, Chen et al published an evaluation of MTBE's impacts specifically on human lymphocytes. They used the alkaline comet test and showed that MTBE can damage the DNA in isolated human lymphocytes. They found that MTBE caused the DNA strands to break. According to the researchers, "the results obtained suggested that MTBE and BTEX could induce a variety type of DNA damage such as single-strand breaks, double-strand breaks, and oxidative base modification". The Chen et al results support observations of leukemia and lymphoma, as do previous genotoxicity studies, including the study carried out by industry in 1980, as discussed above.

The fact that strand breaks were observed by Chen et al. is particularly troubling because these can result in large pieces of DNA being misaligned, lost, or otherwise malfunctioning. Strands of DNA carrying thousands of highly specific directions for how the body function. Strand breaks in heritable cells (i.e., in the DNA in eggs and sperm) can lead to such severe disruption of development that a fetus does not survive. Strand breaks are also the subject of considerable study as causes of cancer.

The genotoxicity studies contribute to our scientific understanding of how MTBE behaves in the body. Understanding the mechanisms by which MTBE acts support the plausibility of the cancer results obtained in the long term exposure studies. They strengthen the overall weight of evidence regarding MTBE carcinogenicity, as described in USEPA's cancer assessment guidelines (USEPA, 2005).

Industry was first put on notice that MTBE could be genotoxic based on the results of the 1980 ARCO study. The studies in the 1990s and more recently confirm the early findings and indicate a potential to cause cancer and birth defects.

Based on the studies listed above, I conclude MTBE is genotoxic and can cause mutations. The studies are also the type that USEPA specifically lists as being relevant when deciding if a chemical is a carcinogen and whether it has genotoxic capabilities (USEPA, 2005). Determining whether MTBE is genotoxic is a critical element in determining whether there could ever be a "safe" level of exposure. It is widely held that chemicals which are genotoxic and cause cancer pose some level of risk at any exposure level (USEPA, 2005). Clearly, a chemical that can cause mutations poses a risk to present and future generations.

The widespread MTBE contamination, evidence that MTBE in genotoxic, and the related fact that there is no safe level of exposure to a genotoxic carcinogen are key factors in forming my opinion that MTBE poses a human health hazard and that there is no "safe" level of exposure. The many other hazards outlined in this report contribute substantially to my concern regarding

the potential of MTBE to cause birth defects and damage peoples' liver, kidneys, and other parts of their bodies. The fact that MTBE is capable of causing cancer in multiple organs adds scientific credence to the conclusion that MTBE is inherently unsafe and that all possible steps should be taken to remove it from drinking water.

Summary Regarding Cancer and Mutations.
Overall, it is clear that MTBE can cause both mutations and cancer.[22] MTBE also causes pathological changes in the ability of the body to defend against these types of damage. From the initial studies, including the 1980 ARCO study, though the studies reported in 1991 showing cancer, the scientific evidence would lead responsible scientists to conclude that MTBE could cause mutations and cancer. Likewise, MTBE's metabolite, formaldehyde, is a long-established mutagen and carcinogen. Another metabolite, TBA was found to be carcinogenic in the 1980s.

Given industry awareness of study results showing MTBE and its metabolites cause mutations and cancer, they should have taken every possible precaution to avoid exposing the public to MTBE. Their various claims that MTBE is not carcinogenic are disingenuous, given the substantial evidence to the contrary. Additional efforts to confuse the issue by raising technical objections that are not appropriate further delayed responsible actions by the government.

Conclusions that would logically be drawn from the above are:

- Early evidence regarding MTBE's ability to cause mutations, as well as its metabolites cancer-causing abilities, should have led industry to suspect MTBE would be carcinogenic.

- Industry-sponsored studies that showed multiple cancers in multiple species put industry on notice regarding a very serious potential for harm to human health.

- Delays in publishing their cancer studies and unwarranted arguments regarding the value and validity of studies that showed MTBE was a carcinogen created confusion and delayed protective and appropriate action by government agencies.

- In light of the cancer evidence, it was irresponsible for industry to market and distribute MTBE, given their knowledge that the public would be exposed to it via drinking water.

- The early evidence of MTBE's carcinogenicity was available to industry at a time when it was still making decisions about what oxygenate or oxygenates to use to comply with RFG requirements.

22 My opinion regarding the carcinogenic potential of MTBE does not depend on any single study, but rather relies on the overall weight of evidence regarding cancer, in keeping with the USEPA guidelines on evaluating carcinogens (USEPA, 2005).

G. MTBE's Metabolites.

MTBE metabolites, formaldehyde and TBA, are carcinogenic and have other hazardous properties. Formaldehyde is also a known carcinogen. TBA was also known to be hazardous early in the development of MTBE as a gasoline additive and a 1995 study by the National Toxicology Program (National Institutes of Health) found TBA in drinking water caused an increase in kidney and thyroid cancer (NTP, 1995).

Industry was aware of these metabolites and speculated that MTBE's toxic properties might be due to its metabolites. A 1987 memo from Exxon to OFA outlined the "comparative genotox activity of MTBE and Formaldehyde" stating that: "formaldehyde has been active in a variety of in vitro mutation assays (i.e., mouse lymphoma, etc.)." (Lington, 1987). So clearly the potential for causing mutations and therefore, for carcinogenic action was known or suspected. Both the knowledge of formaldehyde that industry had, and their early study results showing mutagenic effects on lymphocytes (ARCO, 1980) should have put industry on notice in the early 1980s that MTBE might cause cancer. Industry repeated statements that MTBE was not mutagenic, and emphasized studies that did not show harm. Ignoring existing evidence and failing to follow up with stronger studies when results were equivocal was irresponsible. Industry had sufficient information that MTBE could pose a risk to the public.

The mutation study described above found that mutations occurred when MTBE was converted to its metabolites. Industry also speculated that MTBE's metabolites might play a key role in causing the results seen in the cancer studies. Therefore, industry knew that the results of the genotoxicity study could be quite important, that it supported the findings of their own cancer studies, and that this information could be used together to form a stronger basis for arguing that MTBE causes cancer.

It is also noteworthy that the problems of incomplete reporting, and inadequate study design, discussed in the section on reproductive and developmental damage above, are also seen in the genotoxicity studies.

H. Disruption of Normal Hormone Function.

The disruption of hormones, often referred to as "endocrine disruption", is now a well recognized problem that must be given consideration when evaluating health hazards of chemicals. As described above, the Faroes statement urges substantial caution from leading scientists and pediatric health specialists in this area due to the potential for harm to children. Endocrine disruption is complex to study because it often does not exhibit a standard toxicological dynamic of increasing effect with increasing dose (Andrade, et al, 2006).

In females, Moser et al (1998) found that MTBE caused endocrine (hormone) disruption and decreased the weights of ovaries (the female reproductive system) and pituitary glands. MTBE caused abnormal reproductive cycles in females (prolonged estrous cycles) and "multiple endocrine-related tissue and cellular responses" (Moser et al, 1998). This indicates that MTBE

effects already known about chemicals with a similar composition. MTBE is a member of the ether family based on its composition, and industry has likewise discussed it as a member of the ether family (Kirwin, 1979). Industry clearly knew MTBE was likely to cause a variety of health problems and in fact had observed some of these in their employees who worked with MTBE. MTBE also has solvent properties. Both ethers and solvents have other long-standing and well-known health hazards including damage to the nervous system. A brief summary is provided below to illustrate what was known about solvents and ethers prior to the use of MTBE in gasoline.

Ethers have been used in medicine (e.g., as an anesthetic) for over 100 years and so reports and studies about ether's toxic properties are extensive. Standard reference books for toxicologists from the 40s and 50s documented ether's ability to cause damage to the nervous system, damage to blood cells, and many other adverse effects (Lehmann and Flury, 1943, Fairhall, 1957). There were also studies carried out in the US and other countries that identified increased rates of spontaneous abortions, birth defects, and other reproductive effects, as well as numerous types of organ damage and disease among workers who used ethers in medical settings (Spierdijk et al, 1976). The reproductive toxicity of glycol ethers was also well established (Hardin, 1983).

MTBE is a solvent and solvents are defined by their ability to dissolve and penetrate things, rather than their chemical structure. MTBE had been used to a limited degree as a solvent prior to its use in gasoline. Solvents are known for their ability to pass through the walls of cells because they can dissolve the lipid elements of cell walls. They can move throughout the body and cause particular disruption and damage to organs and structures with a high considerable fat content (Lehmann and Flury, 1943). These include bone marrow (relevant to blood formation and leukemia), nerve cells (most are lipid coated), and many other structures.

The liver, kidneys, blood vessels, and heart were also considered major target organs, and pregnant women were considered "especially endangered" with solvents recognized as being capable of penetrating the placenta and reaching the fetus (Lehmann and Flury, 1943). Many more recent publications document these and other hazards of solvents.

The fact that MTBE is a member of the ether family and behaves like a solvent as well is reason for serious concern regarding its potential for harm. Information on ethers and solvents was widely available and known among toxicologists and those working on health risk evaluations. This information put industry on notice prior to the use of MTBE in gasoline that the potential for MTBE to cause harm was considerable.

M. Health Hazards Summary

The information discussed above clearly shows that MTBE can cause many different types of harm, including harm to the nervous system, immune system, kidneys, liver, lungs, reproduction, and normal growth and development. It is clear that MTBE is a carcinogen and is genotoxic. The general scientific consensus is that studies in animals can predict the types of harm that will occur in humans with a good degree of certainty (USEPA, 2005), so the evidence from animal

studies should be relied upon to make the decision that MTBE exposure is not safe.

Information on the harm that could be caused by MTBE's metabolites and its chemical families was available prior to industry adding MTBE to gasoline. The studies in the early 1980s confirmed the toxicity of MTBE and provided evidence that MTBE could cause a variety of health problems. The information discussed above and other scientific information on MTBE[23] forms a coherent pattern of toxicity with respect to the kinds of harm MTBE could cause. So the hazardous nature of MTBE would be understood by toxicologists and others trained to evaluate chemical hazards.

There are areas where uncertainties prevail, as with developmental and reproductive toxicity, neurotoxicity, immunotoxicity, and endocrine disruption make it impossible to "predict" a safe level of exposure, even in the absence of evidence regarding MTBE's carcinogenicity and genotoxicity. The strong evidence regarding cancer and genetic damage clarify that there is no completely safe exposure level.

There is a need to consider quantitative data and dynamics in both the science and public policy aspects of chemical management; however, protecting public health often entails evaluations that go far beyond simple calculations. Careful consideration of hazards, susceptible populations, and the uncertainties inherent in health evaluations are equally relevant and in the case of MTBE clarify the need for caution and exposure reduction, to the maximum degree possible.

In summary:

- MTBE caused a variety of health effects in scientifically credible studies carried out in multiple species of animals via multiple routes of exposure (inhalation, ingestion, skin exposure). The results indicate that MTBE can damage most organ systems in the body.
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- MTBE caused multiple types of cancer in multiple study species. Genotoxicity and other studies provide additional evidence that it is a carcinogen. Scientific consensus and federal policy establishes that there is no safe level of exposure to carcinogens that act via genetic damage.

- Scientific consensus and federal policy establishes that children are at greater risk than adults when they are exposed to most carcinogens and merit special protection. They are also considered more susceptible to other types of harm, including neurotoxic effects.

- MTBE caused numerous birth defects in developmental and reproductive studies indicating a need for protecting people from exposure during development.

- Other sensitive subpopulations including the elderly are likely to disproportionately suffer

23. Reference is made to the substantial scientific data available in the peer-reviewed literature, in documents describing privately-funded studies that were provided to USEPA, and to other toxicological, epidemiological and related studies of MTBE and its metabolites and structural analogs (chemical family).

ill effects from MTBE because they already have conditions that put them at greater risk from exposure to MTBE than the average healthy adult.

- Industry-sponsored and had access to study results indicating early on that there was a likelihood that MTBE could cause serious health hazards, including cancer.

- The way that industry reported study results was misleading in not alerting the public to key hazard information.

- The delays in reporting important studies that showed MTBE caused cancer and other serious effects limited the ability of the public to make informed decisions regarding MTBE.

- Extensive and long-standing scientific evidence regarding ethers, solvents, and evidence regarding MTBE breakdown products, formaldehyde and TBA, put industry on notice that MTBE could cause foreseeable health hazards. MTBE in drinking water poses health hazards that include cancer and death. There is no safe level of exposure to MTBE and consequently it is both reasonable and responsible to strive for elimination of MTBE from drinking water supplies.